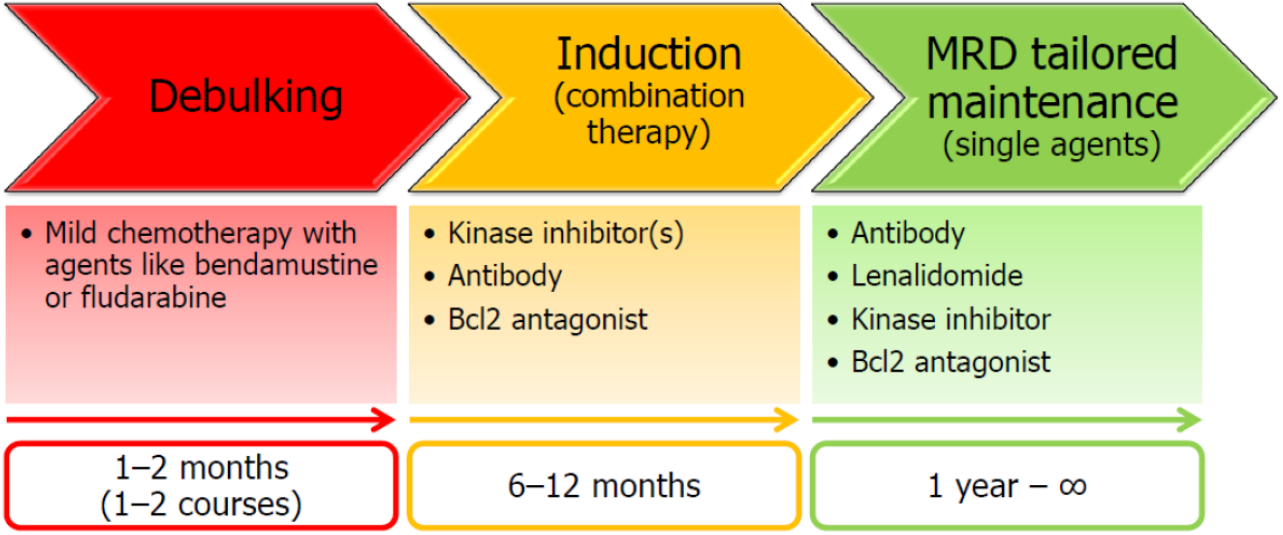
Význam minimální reziduální nemoci u chronické lymfocytární leukemie



Michael Doubek

II. český hematologický a transfuziologický sjezd, 14. 9. 2021

Interní hematologická a onkologická klinika
FN Brno a LF MU
Department of Internal Medicine, Hematology and Oncology,
University Hospital Brno
and Masaryk University, School of Medicine

ČS CLL
Česká skupina pro chronickou lymfocytární leukémii

MUNI MED

FAKULTNÍ NEMOCNICE BRNO

CELL
the CzEch leukemia study group for life

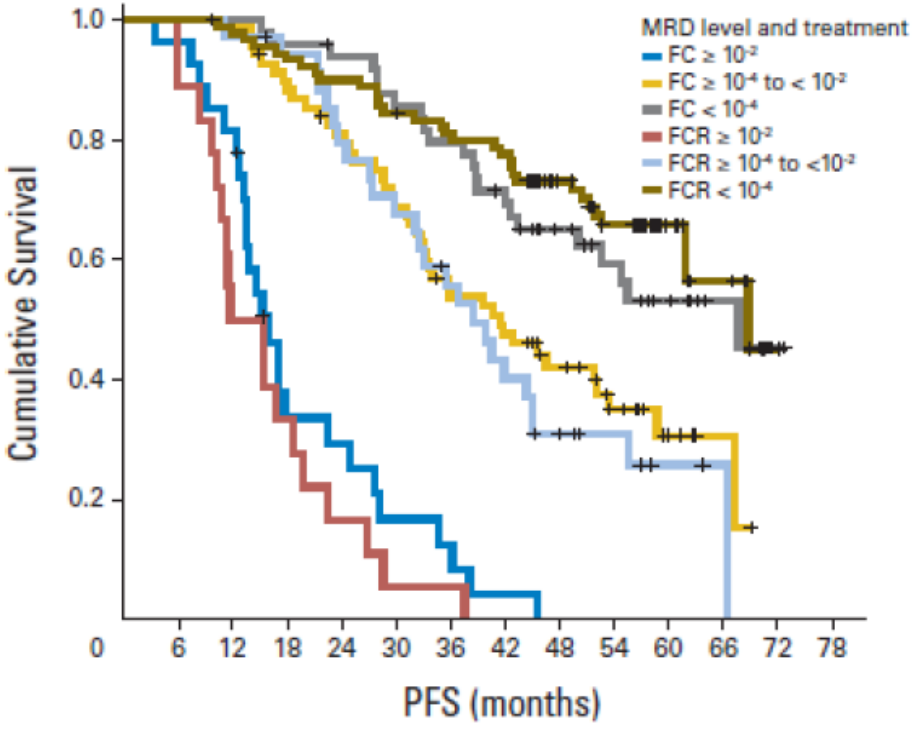
CEITEC

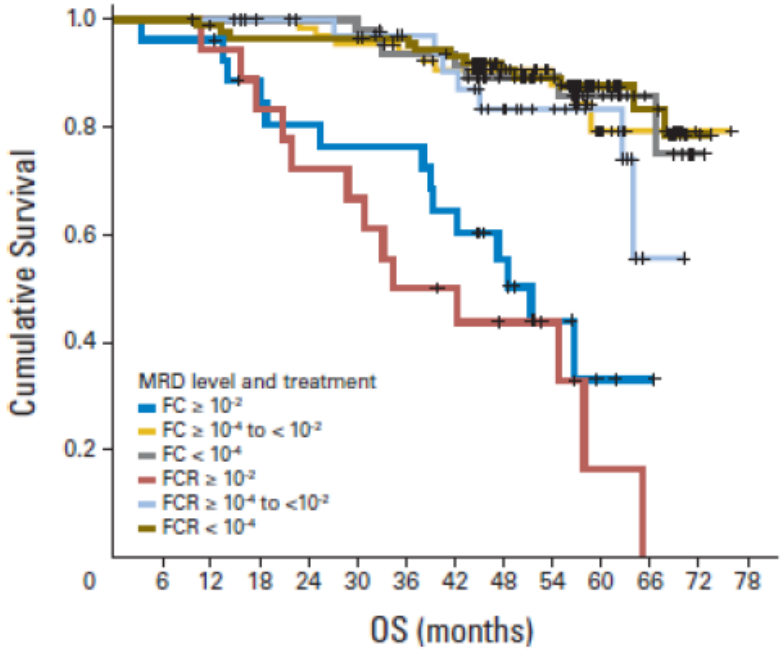
Prohlášení o spolupráci s farmaceutickým průmyslem

Podpora výzkumu: AbbVie, AOP Orphan, Roche, Novartis, Gilead, Sandoz
Zaměstanec: Ne
Konzultant: AstraZeneca, AbbVie, Janssen, Novartis, Roche, Gilead
Akcionář: Ne
Advisory Board: AbbVie, AOP Orphan, AstraZeneca, Amgen, AbbVie, Gilead, Janssen, Roche, Novartis

Minimální reziduální nemoc u CLL

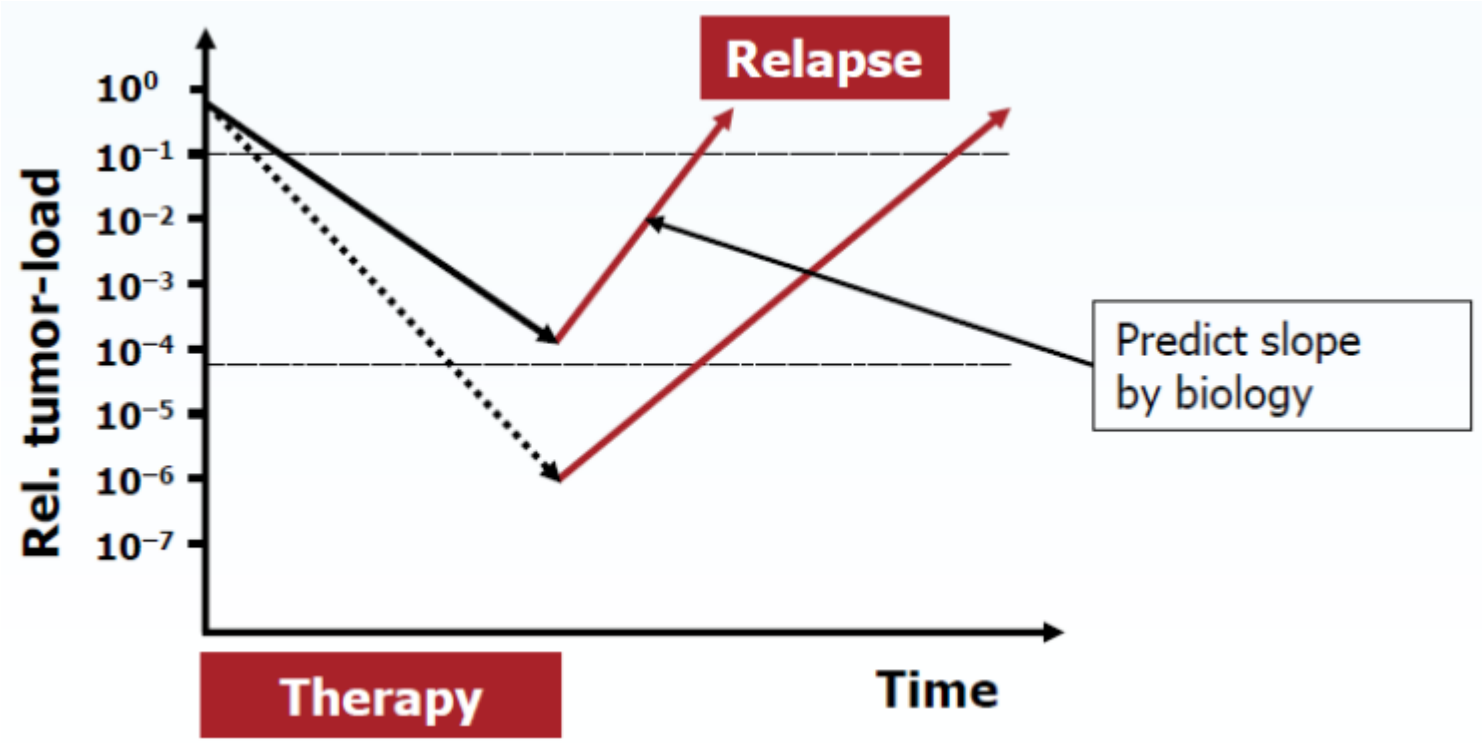
Hladina MRD predikuje výsledek léčby, nezáleží na léčbě jako takové.





Boettcher et al, 2012

MRN



Böttcher S, et al. Hematol Oncol Clin North Am 2013

Léčba CLL 2021 a dále

- Intenzivní léčba cílící na dosažení negativity MRD a vyléčení
  - Kombinace nových léčiv s monoklonálními protilátkami
  - Kombinace nových léčiv navzájem
  - Časově omezená terapie (v 90 % případů je nejhlubší MRD odpověď dosažena do 24 měsíců od zahájení terapie; Mato IWCLL 2019)
  - Méně dlouhodobé toxicity (hypertenze, arytmie)
  - Méně klonální evoluce (mutace ovlivňující vazbu léku, mutace vedoucí k autonomní signalizaci, aktivace alternativních drah, deregulace antiapoptotických drah)

Ibrutinib – rizikové faktory progrese

Predisponující:

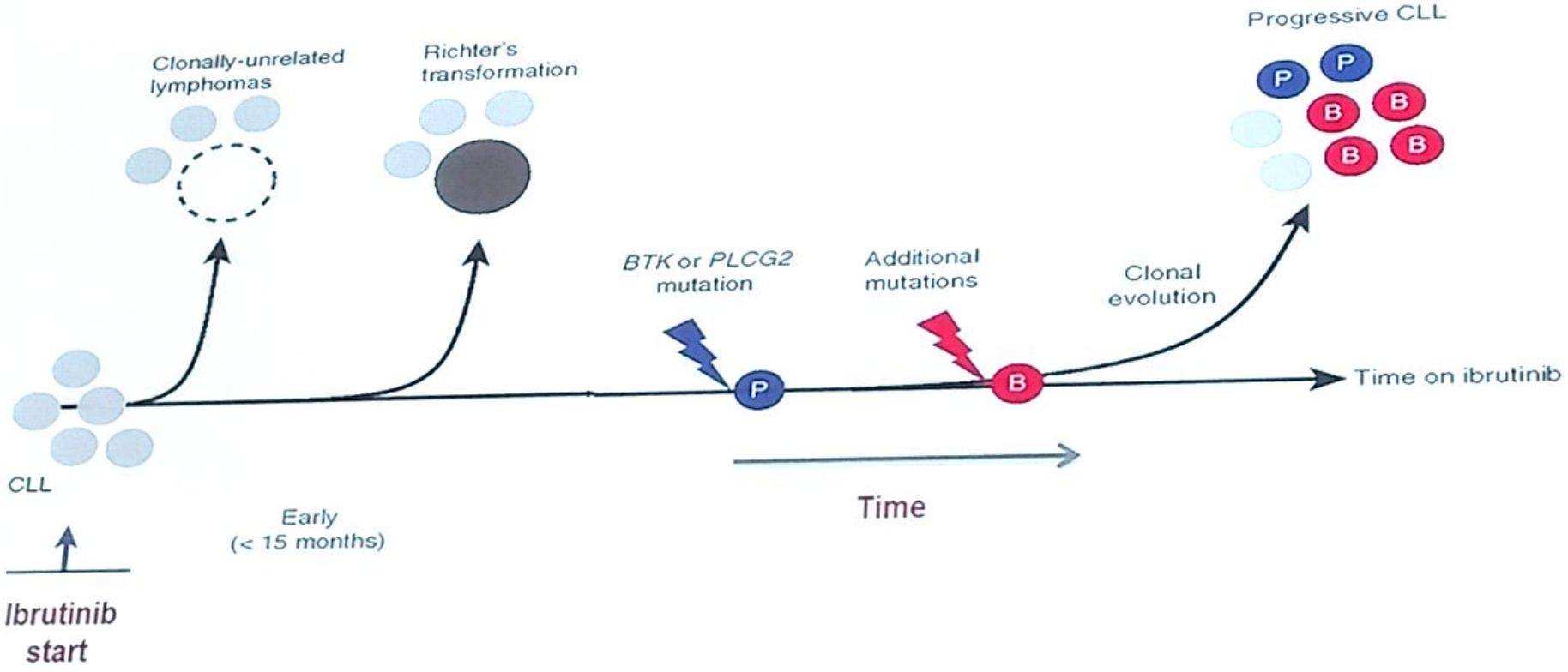
- **del 17p**
- **komplexní karyotyp**
- **vyšší věk**
- **více jak 3 předešlé terapie**

Získané:

- **BTK mutace**
- **PLCg mutace**
- **MYC abnormality**
- **del 8p**
- **trisomie 2p**
- **del 18p**

Rosenquist et al. IWCLL 2017

Mechanismy rezistence na ibrutinib



Woyach a kol., 2014; Woyach a kol., 2017; Jones a kol., 2017

Inhibitory BCR signalizace a riziko Richterovy transformace

Studie	Počet pacientů	Populace pacientů	Léčba	Prevalence RT
Burger 2015	186	Léčba 1. linie	ibrutinib	0 %
Byrd 2014	391	Relabovaní	ibrutinib	1 %
O´Brien 2014	29	Léčba 1. linie	ibrutinib	3 %
Jain 2015	127	R/R	ibrutinib	5 %
Farooqui 2015	51	Del 17p	ibrutinib	6 %
Mato 2016	178	BCRi	ibrutinib/ idelalisib	7 %
Byrd 2013	85	R/R	ibrutinib	8 %

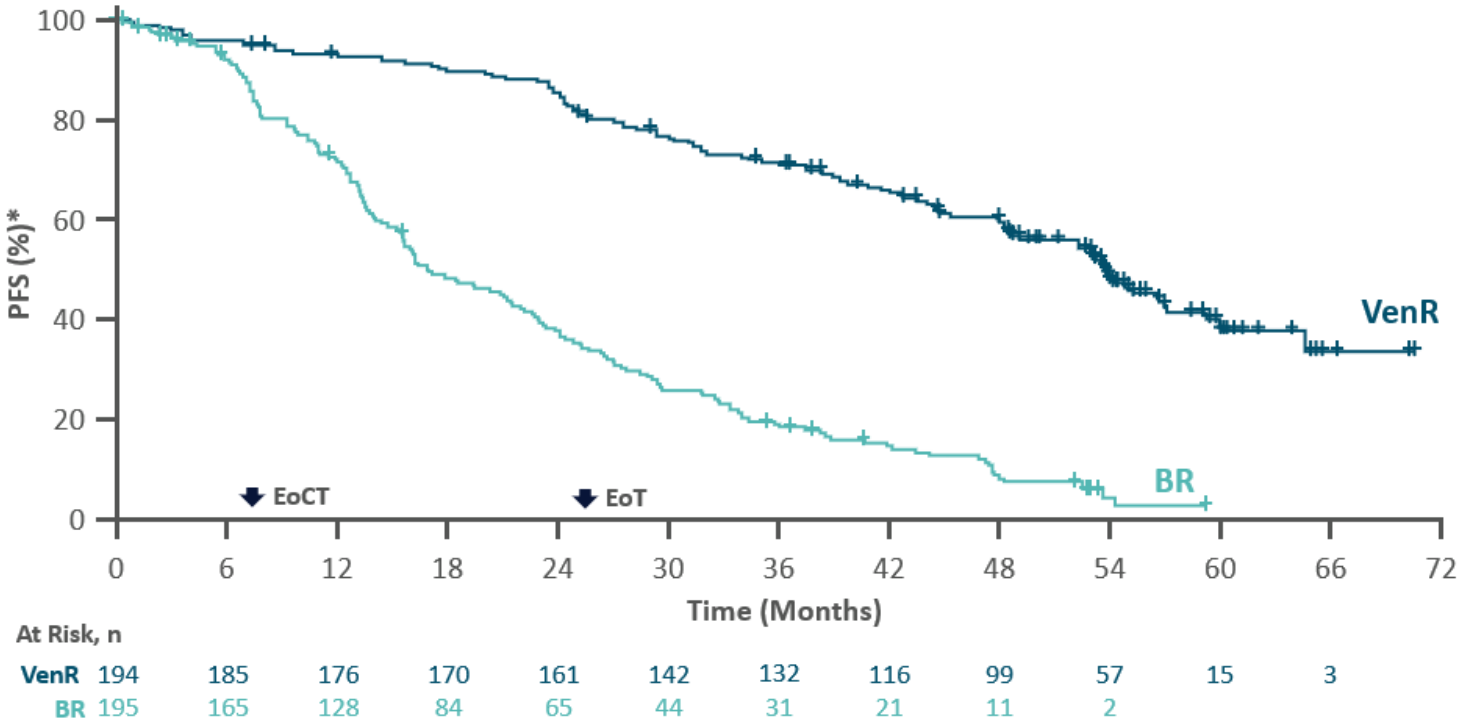
MRN ve studiích

- **R/R CLL**
- **1. linie**

MRN ve studiích R/R

Studie		Populace	Délka terapie 6m 1r	FU (mesíce)	PFS ve 2 letech (%)	ORR (%)	CR/CRi	BM MRD- (%; ITT)	PB MRD- (%; ITT)
MURANO	VR BR	R/R		48	85 36	92 72	27 8		62 13
Obi Ibru Ven	OIV	R/R		16		92	42	58	67
BGB-3111	Zanu	R/R				96	14		
Duve + Ven		R/R				89	33	22	
CLARITY	Ven Ibr	R/R		21		89	27	36	53
COSMOS (tafasitamab)	Ide T Ven T	R/R		12		91 77	9 23		12 46

R/R CLL - VR versus BR - PFS

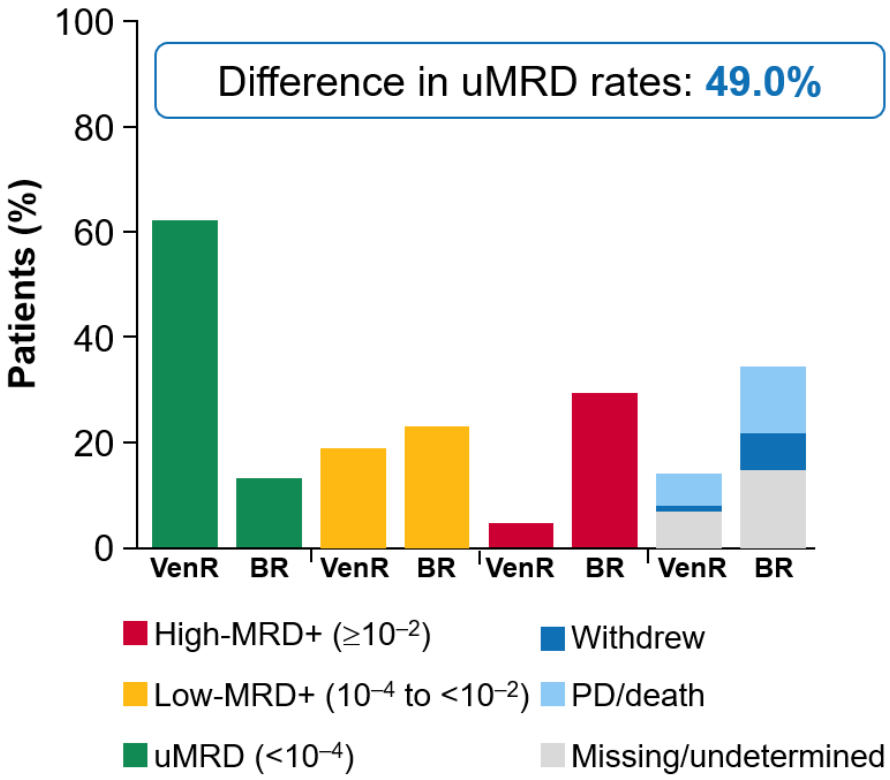


	VenR (n=194)	BR (n=195)
Median PFS, months (95% CI)	53.6 (48.4–57.0)	17.0 (15.5–21.7)
HR (95% CI), p-value	0.19 (0.15–0.26) stratified p<0.0001†	

At the 5-year analysis (median follow-up 59 months), the risk of progression or death was decreased by 81% with VenR vs BR

Kater et al., ASH 2020

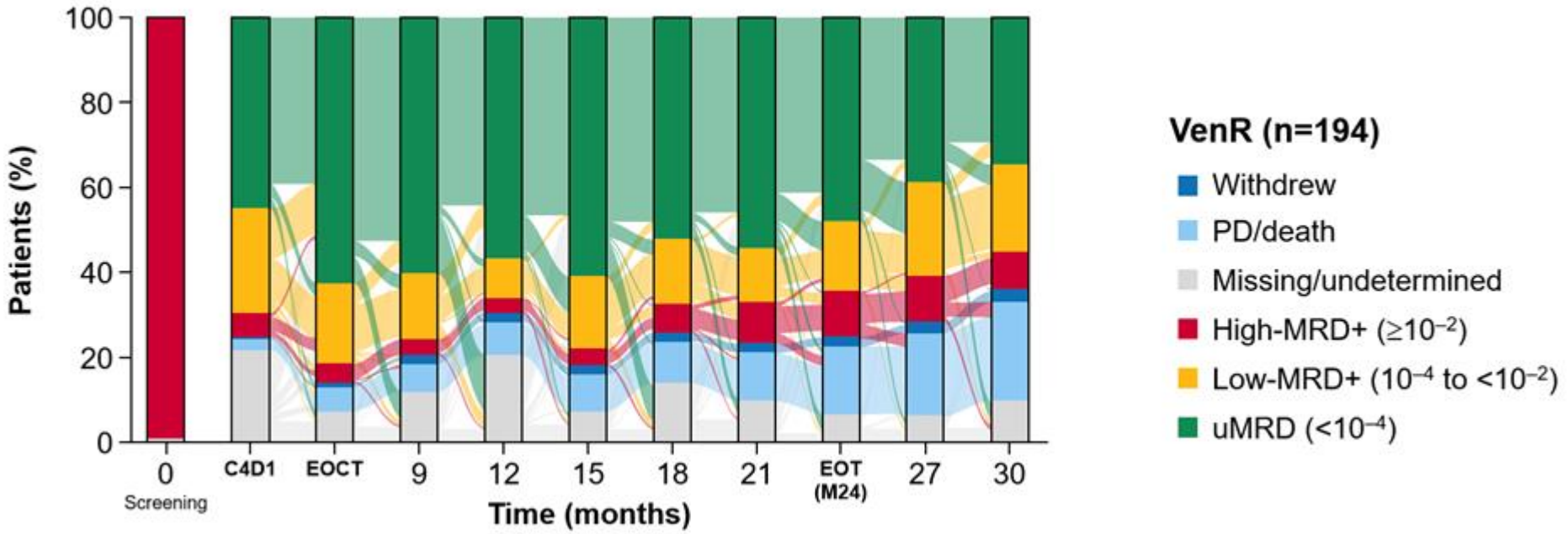
R/R CLL - VR versus BR - PFS



VenR (n=194); BR (n=195)

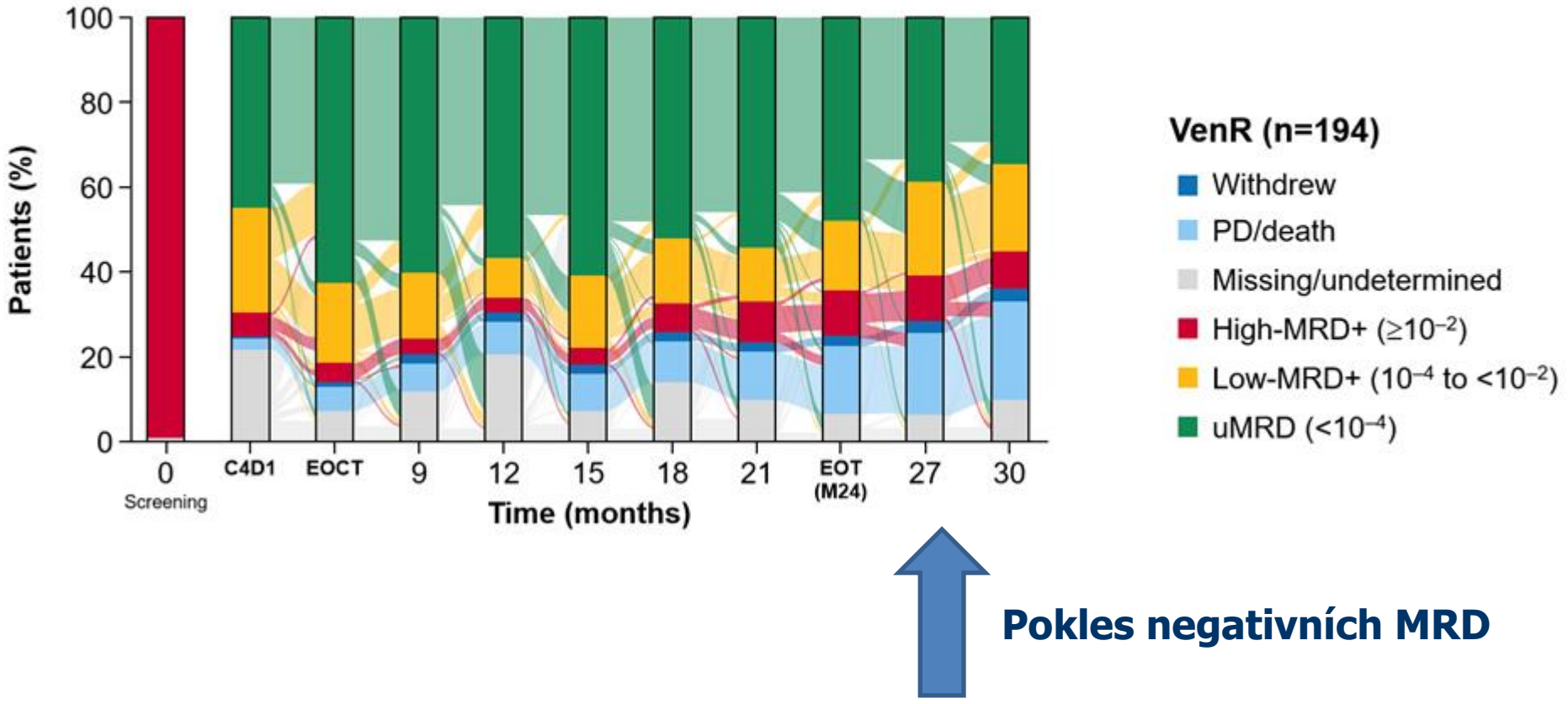
Kater et al., 2018

R/R CLL - VR versus BR - PFS



Kater et al., 2018

R/R CLL - VR versus BR - PFS



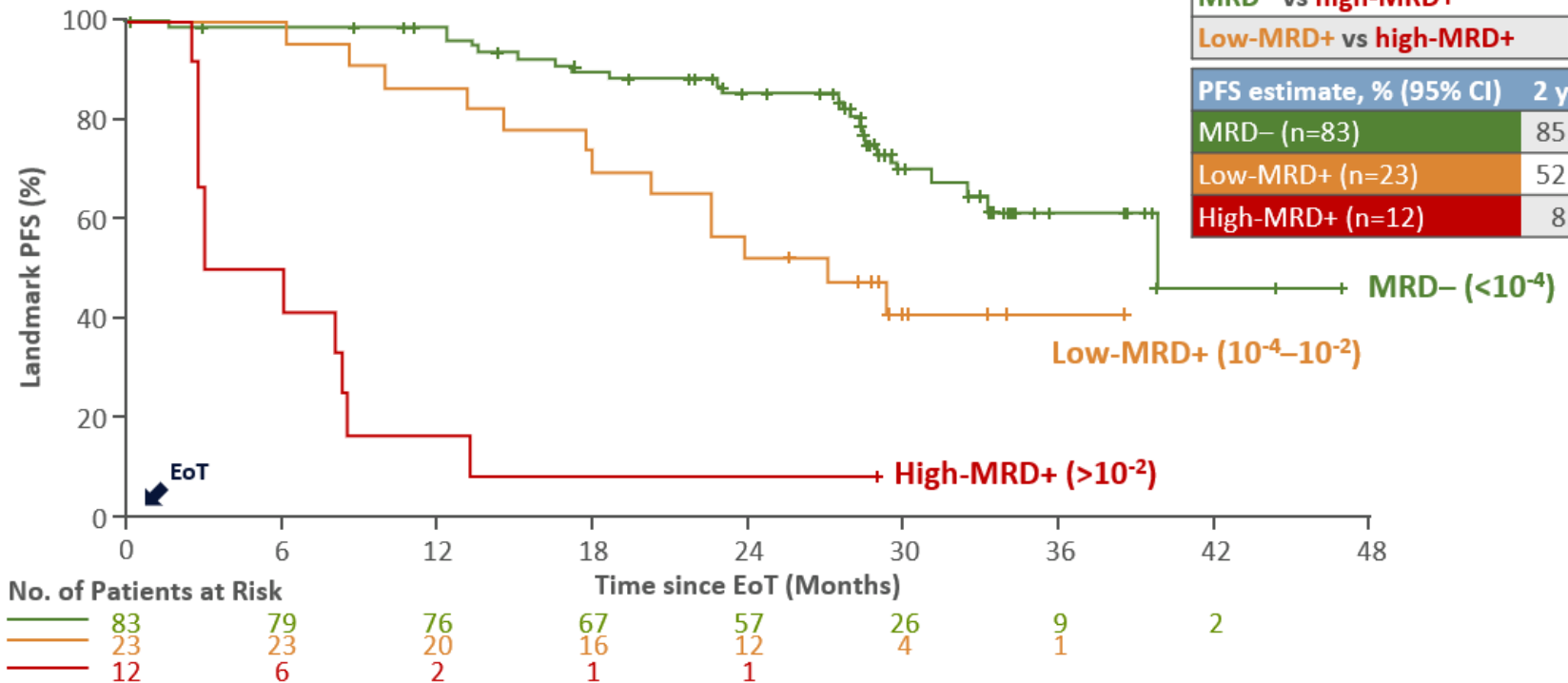
Pokles negativních MRD

Kater et al., 2018

R/R CLL - VR versus BR - PFS

Category	HR (95% CI)	p-value*
MRD– vs low-MRD+	0.40 (0.18–0.91)	0.0246
MRD– vs high-MRD+	0.02 (<0.01–0.18)	<0.0001
Low-MRD+ vs high-MRD+	0.32 (0.10–0.99)	0.0410

PFS estimate, % (95% CI)	2 years after EoT	3 years after EoT
MRD– (n=83)	85.4 (77.4–93.4)	61.3 (47.3–75.2)
Low-MRD+ (n=23)	52.2 (31.8–72.6)	40.7 (19.2–62.2)
High-MRD+ (n=12)	8.3 (0.0–24.0)	NE

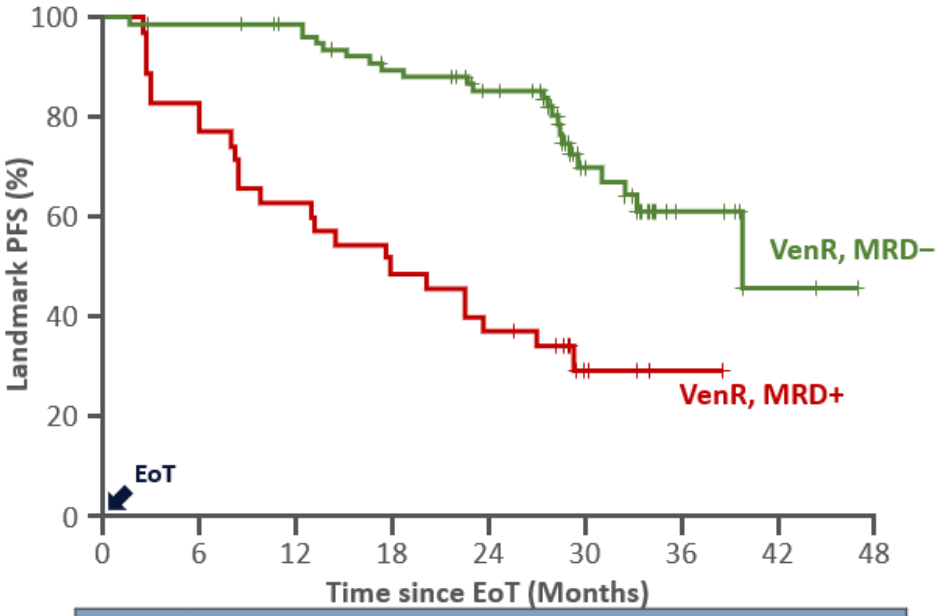


PB MRD– at EoT was associated with longer PFS in the VenR arm, in patients who reached EoT without PD

Kater et al., ASH 2020

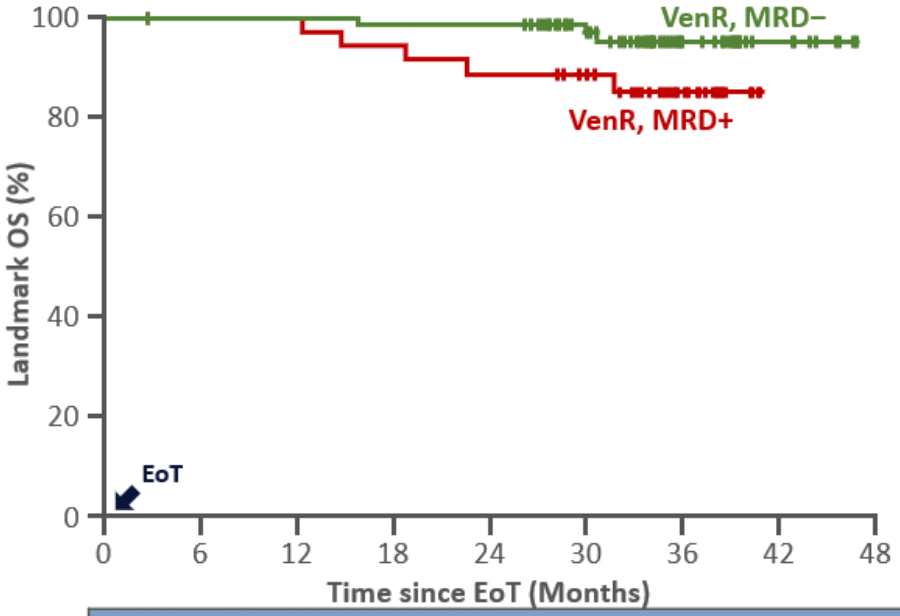
R/R CLL - VR versus BR - PFS

PFS[1]



PFS estimate	2 years after EoT	3 years after EoT
VenR MRD– (n=83)	85.4%	61.3%
VenR MRD+ (n=35)	37.1%	29.2%

OS[2]

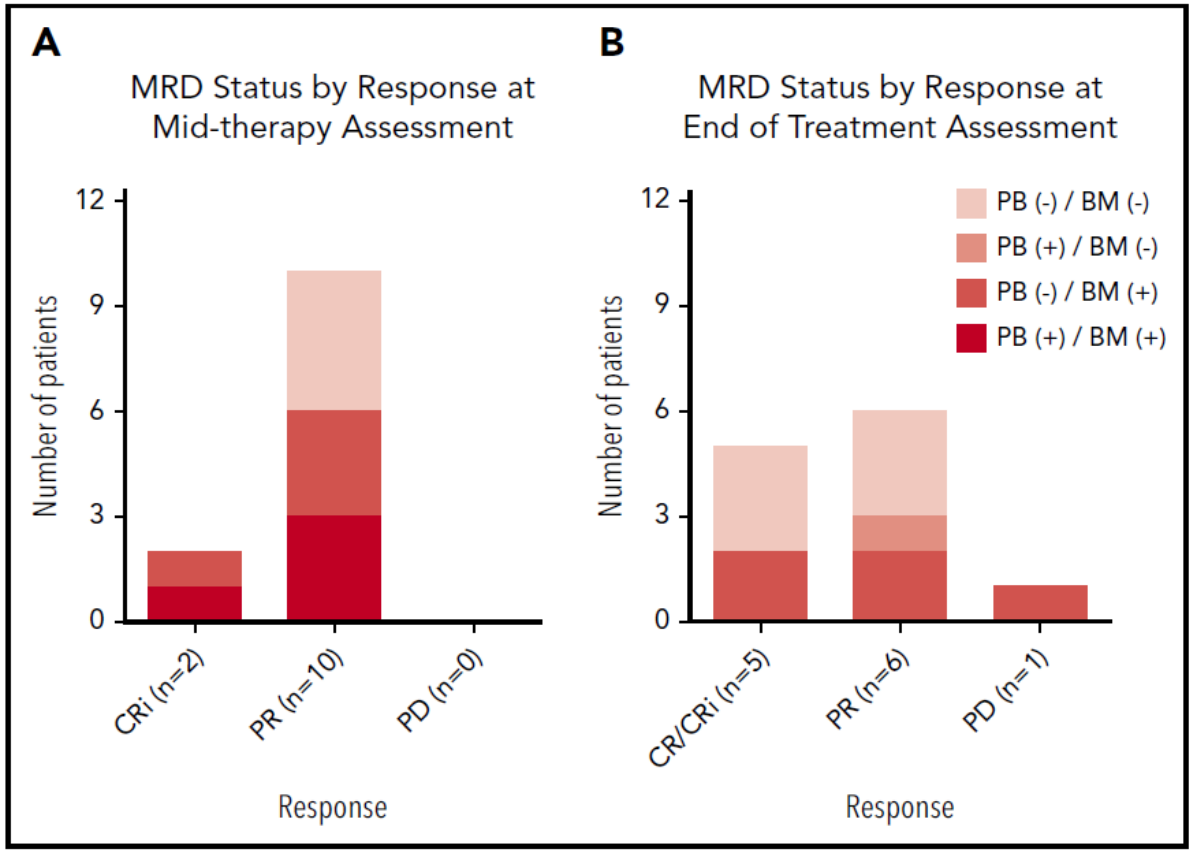


OS estimate	2 years after EoT[1]	3 years after EoT[2]
VenR MRD– (n=83)	98.8%	95.3%
VenR MRD+ (n=35)	88.6%	85.0%

PB MRD– at EoT was associated with improved outcomes post-EoT, in VenR patients who reached EoT without PD

R/R CLL – sekvenční Obi + Ibru + Ven

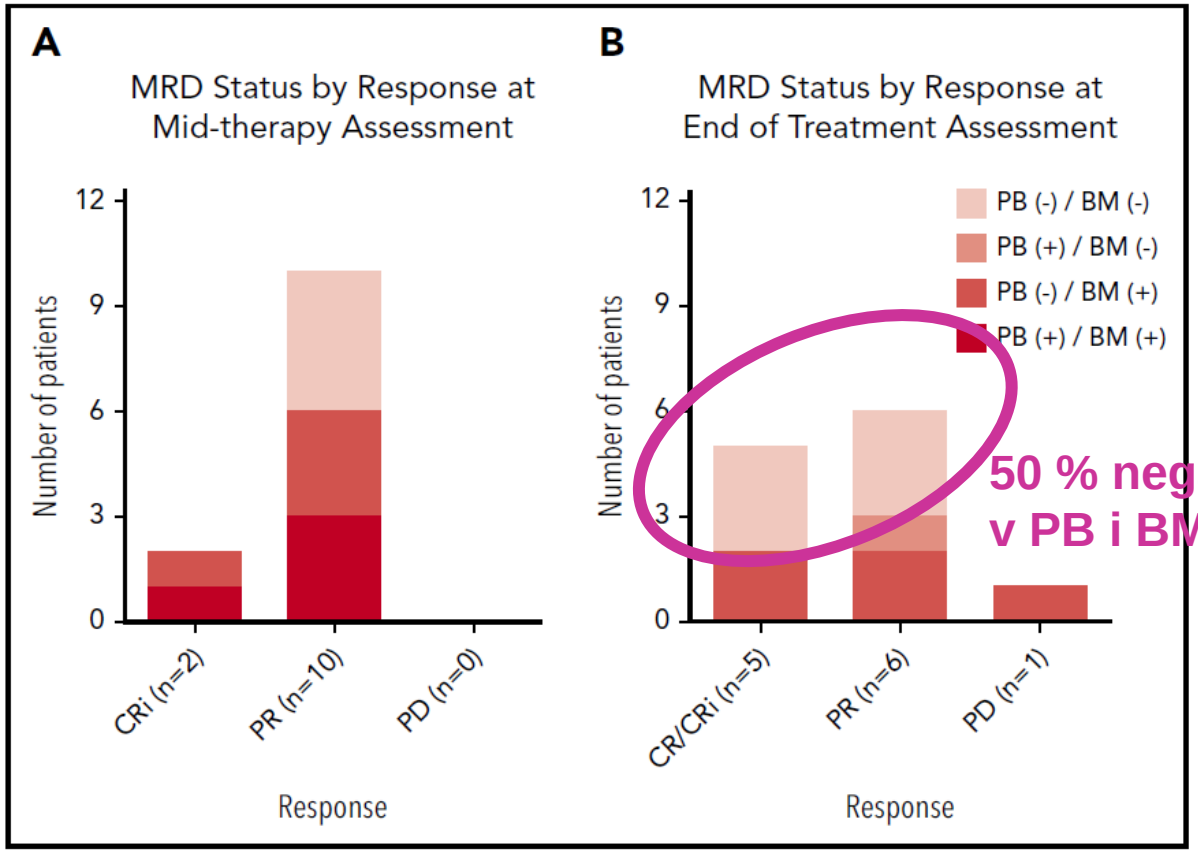
Figure 1. Treatment responses with minimal residual disease status. MRD was assessed by 10-color flow cytometry at both planned response assessments: midtherapy after cycle 8 (A) and end of treatment 2 months after completion of cycle 14 (B). The limit of detection for MRD is less than 1×10^{-4}. BM, bone marrow; PB, peripheral blood.



Rogers et al., Blood 2018

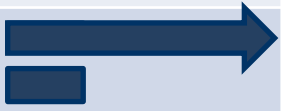
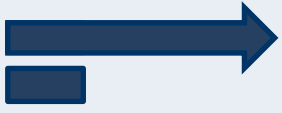
R/R CLL – sekvenční Obi + Ibru + Ven

Figure 1. Treatment responses with minimal residual disease status. MRD was assessed by 10-color flow cytometry at both planned response assessments: midtherapy after cycle 8 (A) and end of treatment 2 months after completion of cycle 14 (B). The limit of detection for MRD is less than 1×10^{-4}. BM, bone marrow; PB, peripheral blood.

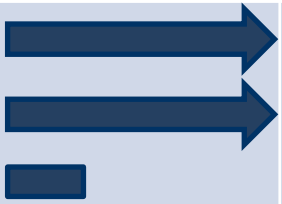
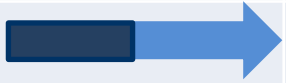


Rogers et al., Blood 2018

MRN ve studiích 1. linie

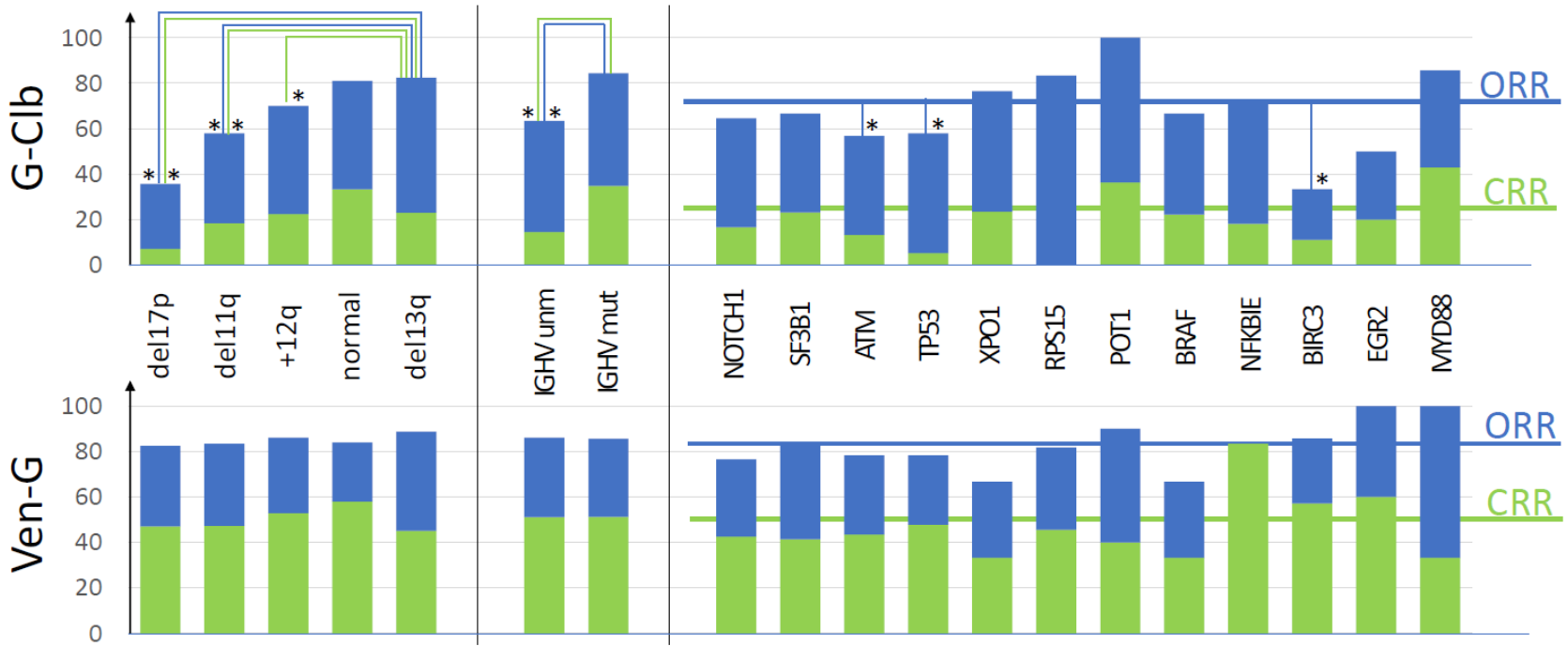
Studie		Populace	Délka terapie 6m 1r	FU (mesíce)	PFS ve 2 letech (%)	ORR (%)	CR/CRi	BM MRD- (%; ITT)	PB MRD- (%; ITT)
CLL14	**VG** **G CLB**	Starší a komorbid.		29	88 64	85 71	50 23	57 37	76 35
CLL11	**G CLB** **R CLB**	Starší a komorbid.		59	60 30	78 65	21 7		38 3
iLLUMINATE	**IG** **G CLB**	Starší nebo komorbid.		31	80 35	88 73	20 8	20 17	30 20
Alliance	**I** **BR**	Starší nebo komorbid.		38	87 74	93 81	7 26	1 8	
CAPTIVATE	**IV**	Do 70 let		16	99	99	92	72	75
FILO	**IG** **(+FC)**	Mladí		16		100	73	79	

MRN ve studiích 1. linie

Studie		Populace	Délka terapie 6m 1r	FU (měsíce)	PFS ve 2 letech (%)	ORR (%)	CR/CRi	BM MRD- (%; ITT)	PB MRD- (%; ITT)
ELEVATE TN	**ACA + Obi ACA Obi-CLB**	Starší nebo komorb.		28	90 82 34	94 85 72			
ACA + OBI + VEN		Mladší a bez komorb.				100	25		65
BGB3111-304 (SEQUOIA)	**Zanu**	Starší nebo komorb.		7		83	0		
E1912	**IR**	Do 70 let		48	93				

CLL14 – Obi-Clb vs. Obi-V

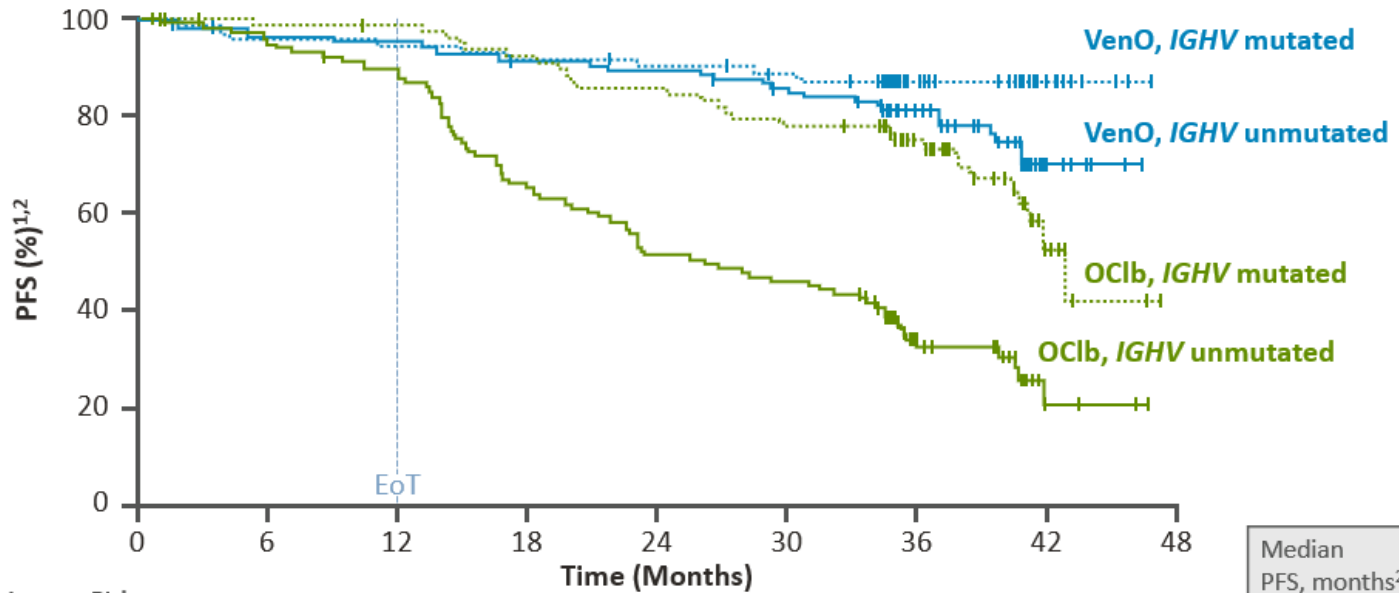
Complete and overall response with G-Clb/Ven-G:



* p<0.05 for each

Tausch et al., 2019

CLL14 – Obi-Clb vs. Obi-V



No. of Patients at Risk:

VenO & *IGHV*^{mut}	76	69	68	66	64	61	37	12	0
VenO & *IGHV*^{unmut}	121	110	109	102	100	94	58	11	0
OClb & *IGHV*^{mut}	83	77	76	71	66	60	44	8	0
OClb & *IGHV*^{unmut}	123	109	100	74	58	52	23	3	0

Median follow-up:
39.6 months (IQR, 36.8–43.0)

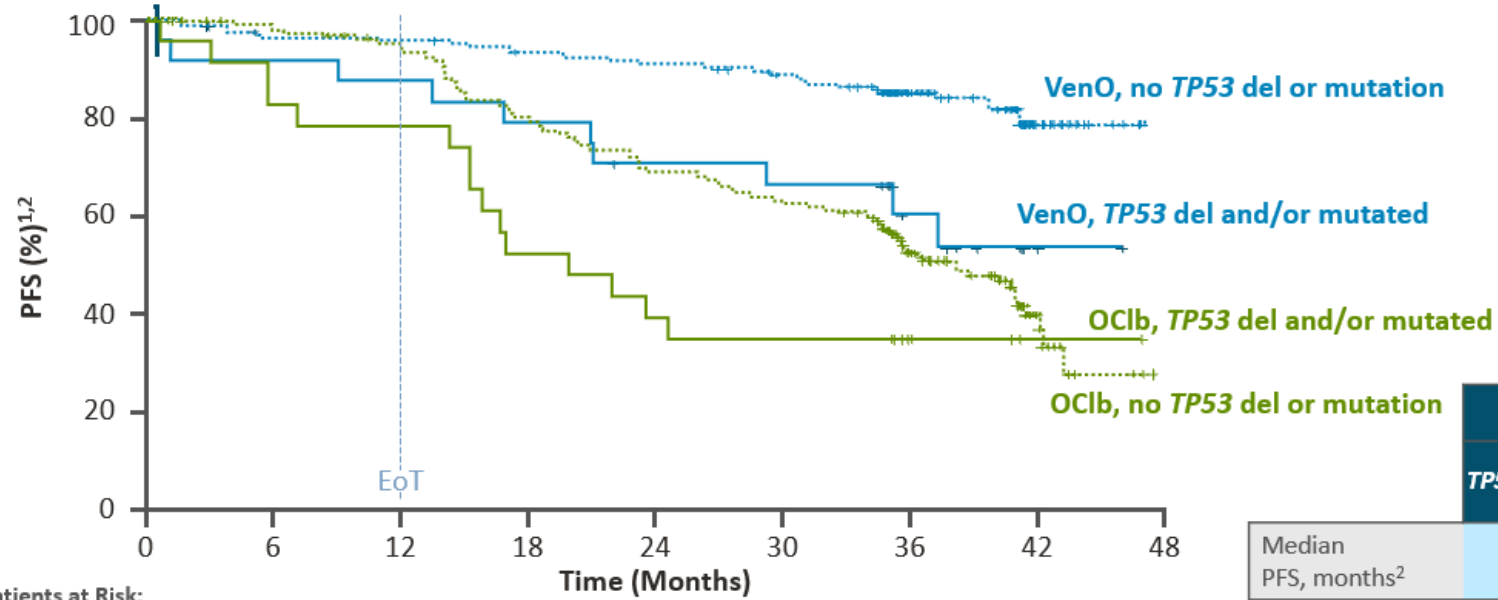
All patients off treatment for ≥2 years

	VenO (n=216)		OClb (n=216)	
	IGHV unmut	*IGHV* mut	*IGHV* unmut	*IGHV* mut
Median PFS, months[2]	NR	NR	26.3	42.9
HR (95% CI)[1,2]	1.96 (0.92–4.17)		2.98 (1.93–4.61)	

With VenO, PFS was comparable for patients with mutated and unmutated *IGHV*.
Regardless of *IGHV* mutation status, VenO was associated with favorable PFS vs OClb

Al Sawaf et al., 2020

CLL14 – Obi-Clb vs. Obi-V



Median follow-up:
39.6 months (IQR, 36.8–43.0)

All patients off treatment for ≥2 years

	VenO (n=216)		OClb (n=216)	
	TP53 none	*TP53* del and/or mut	*TP53* none	*TP53* del and/or mut
Median PFS, months[2]	NR	NR	38.0	19.8
HR (95% CI)[1,2]	3.00 (1.47–6.15)		1.78 (1.03–3.07)	

No. of Patients at Risk:

VenO & *TP53*	25	22	21	19	16	15	9	1	0
VenO & no *TP53*	184	168	167	161	157	149	87	22	0
OClb & *TP53*	24	19	18	12	9	8	3	1	0
OClb & no *TP53*	184	169	160	135	117	106	64	9	0

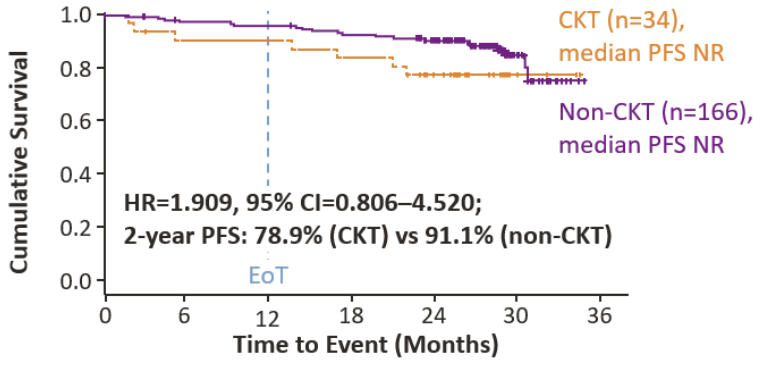
Compared with OClb, the PFS benefit was observed with VenO irrespective of *TP53* deletion and/or mutation status

Al Sawaf et al., 2020

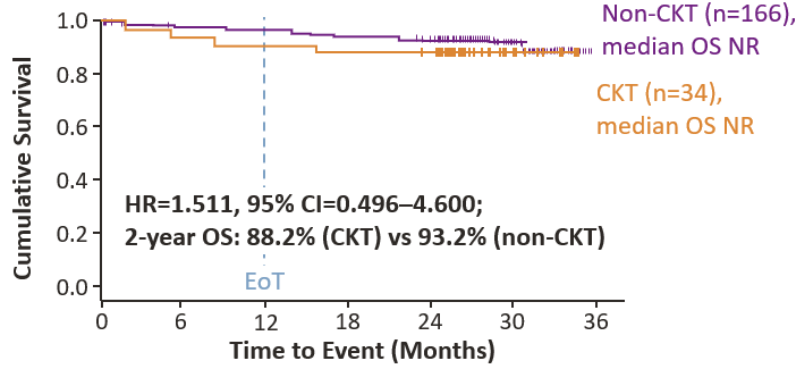
CLL14 – Obi-Clb vs. Obi-V

VenO Arm

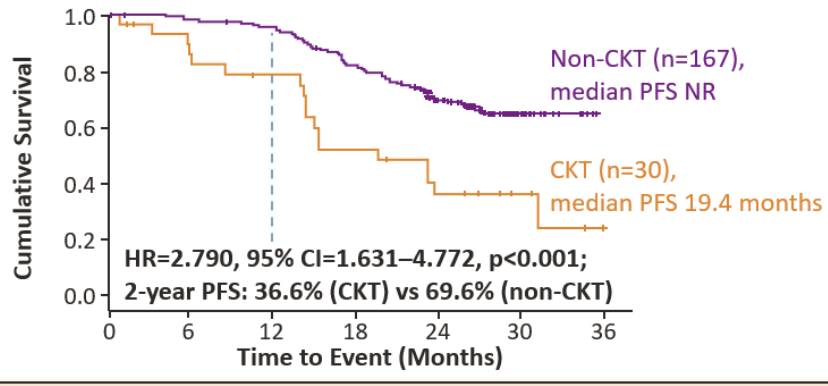
PFS

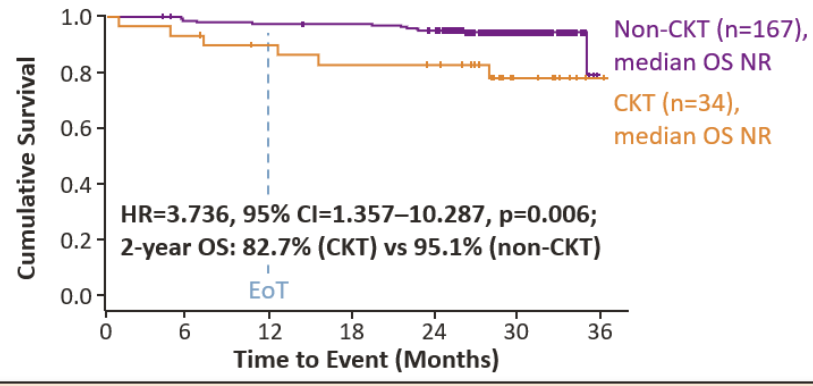


OS



OClb Arm





No difference in PFS/OS was observed between patients with or without CKT when treated with VenO.
Patients with CKT treated with OClb had significantly shorter PFS then patients without CKT

Al Sawaf et al., 2020

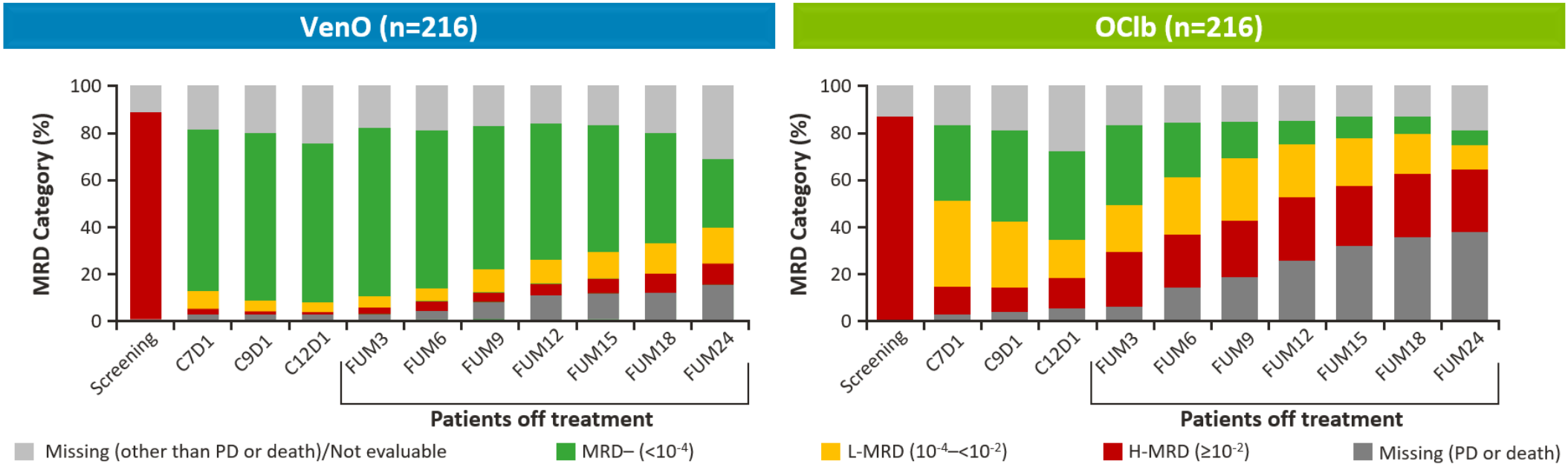
CLL14 – Obi-Clb vs. Obi-V

Minimal residual disease status	**Venetoclax-Obinutuzumab**	**Chlorambucil-Obinutuzumab**	*P* value
Number of patients, N	216	216	
Peripheral blood			
Negative ($<10^{-4}$)	76 %	35 %	< 0.001
Negative ($<10^{-4}$) in complete response	42 %	14 %	< 0.001
Bone marrow			
Negative ($<10^{-4}$)	57 %	17 %	< 0.001
Negative ($<10^{-4}$) in complete response	34 %	11 %	< 0.001

By ASO-PCR 3 months after completion of treatment

Fischer et al., 2019

CLL14 – Obi-Clb vs. Obi-V



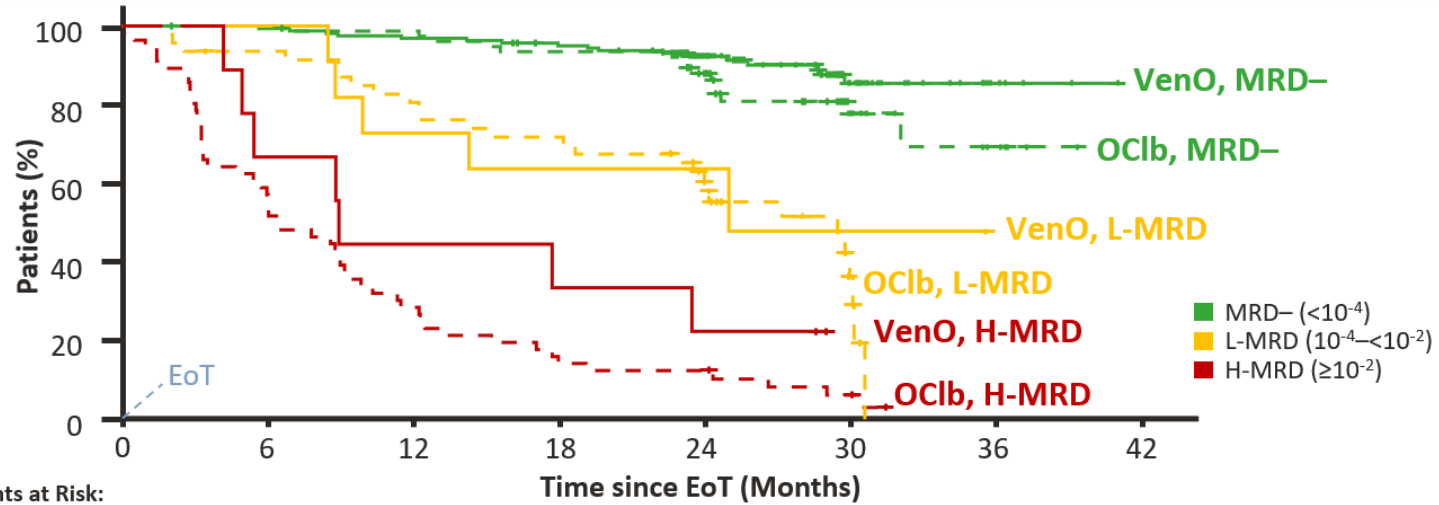
MRD– rate 18 months after EoT: 47% with VenO vs 7% with OClb

MRD– rates were more sustainable after completion of therapy with VenO than with OClb as assessed by ASO-PCR

Al Sawaf et al., 2020

CLL14 – Obi-Clb vs. Obi-V

PFS Landmark Analysis by PB MRD Status (ASO-PCR) at EoT



Median follow-up:
39.6 months (IQR, 36.8–43.0)

All patients off treatment for ≥2 years

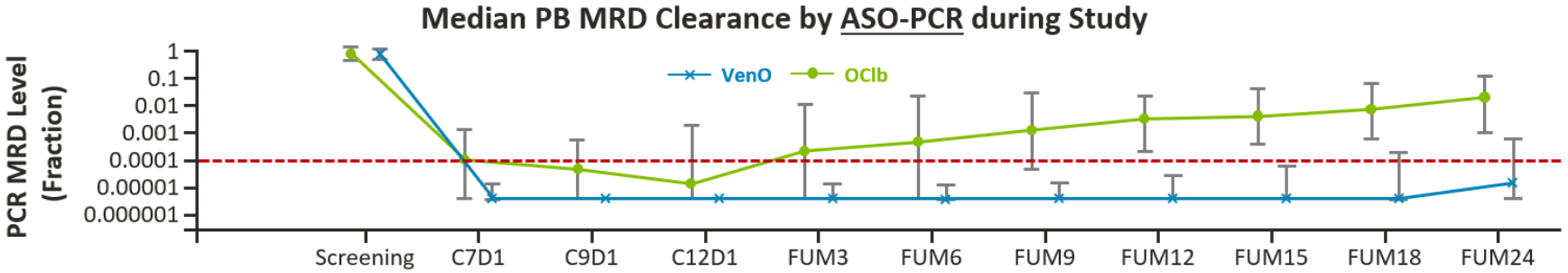
No. of Patients at Risk:

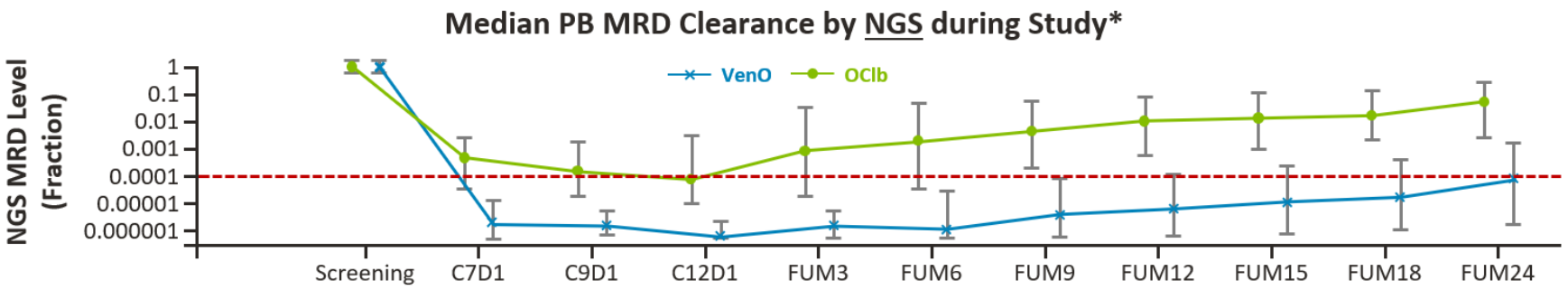
VenO & MRD–	163	161	156	150	91	34	5	0
VenO & L-MRD	11	11	8	7	4	1	0	0
VenO & H-MRD	9	6	4	3	2	0	0	0
OClb & MRD–	76	76	75	71	56	18	6	0
OClb & L-MRD	47	43	37	33	23	5	0	0
OClb & H-MRD	56	32	16	8	7	3	0	0

In a landmark analysis from end of treatment, MRD– patients had longer PFS vs L- or H-MRD patients (HR=0.10; 95% CI=0.06–0.15)

Al Sawaf et al., 2020

CLL14 – Obi-Clb vs. Obi-V

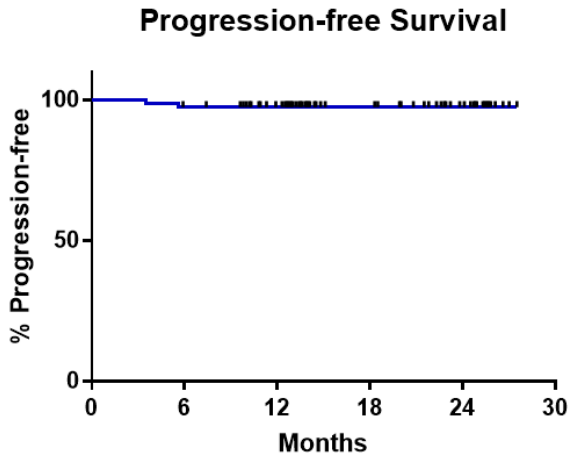


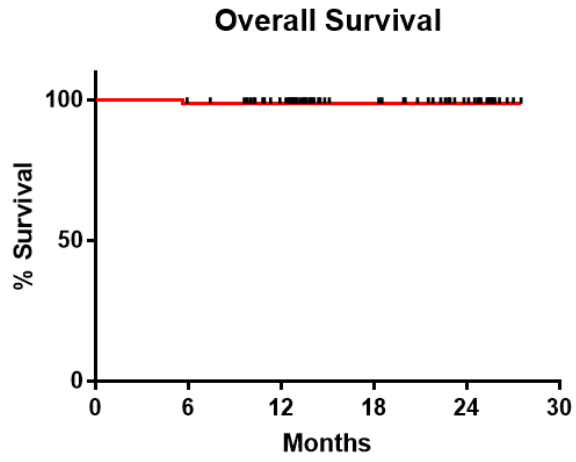


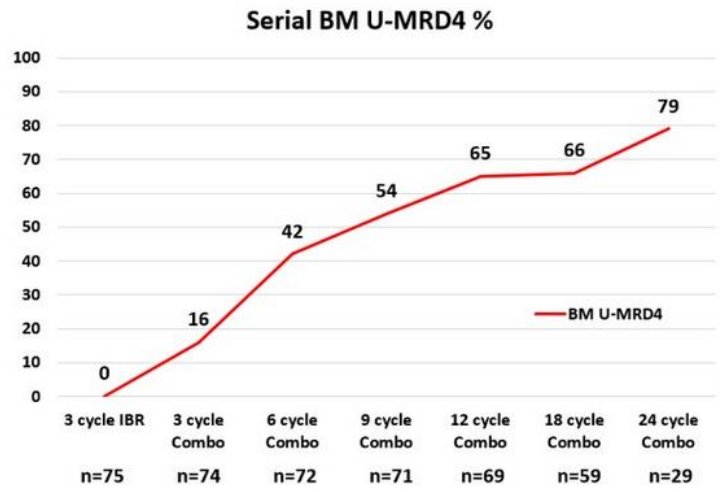
MRD– rates were more sustainable after completion of treatment with VenO than with OClb as assessed by ASO-PCR and confirmed by NGS

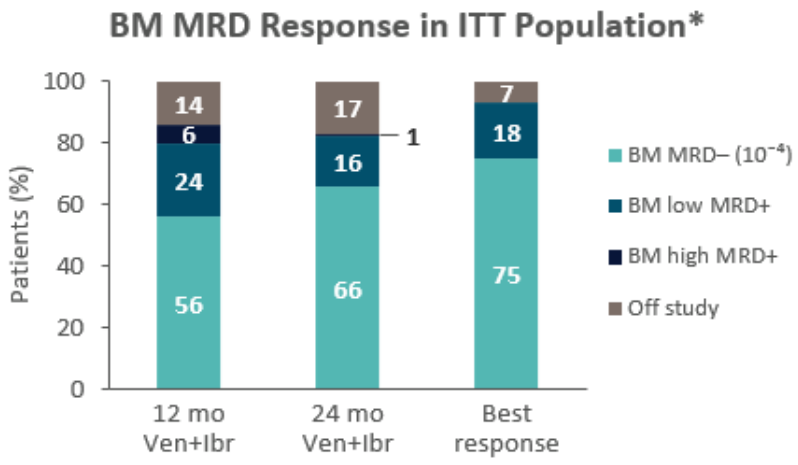
Al Sawaf et al., 2020

První linie – IBRU+VEN – PFS a OS









Jain et al., ASH 2020

Jak MRN vyšetřovat?

- **ASO IGH RQ-PCR - LOD až 10^{-6}**
- **Flow - LOD až 10^{-5}**

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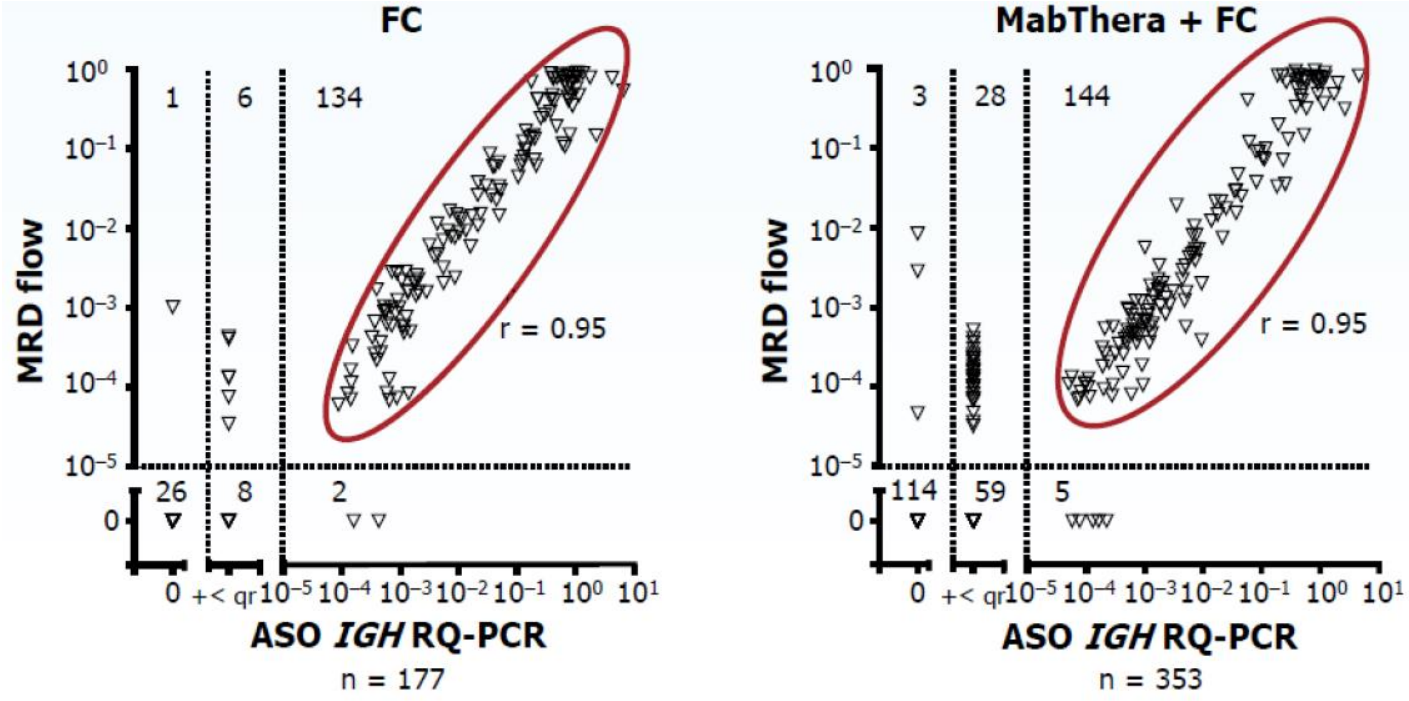


Böttcher S et al. 2009

Jak MRN vyšetřovat?

- **ASO IGH RQ-PCR - LOD až 10^{-6}**
- **Flow - LOD až 10^{-5}**
- **Periferní krev nebo kostní dřeň?**

Jak MRN vyšetřovat?

		FCM-based	PCR-based
Method	reported	multicolor FCM with different antigens (≥4-color)	ASO-RQ-PCR, HTS
	advantage	easy, needs a shorter time	high sensitivity (10^{-5}~10^{-6})
	disadvantage	relatively low sensitivity (10^{-4}~10^{-5})	laborious, time-consuming
Requirement for materials		fresh, living cells, or possibly properly cryo-preserved mononuclear cells (<48 hours after collection)	do not need fresh samples able to conduct with preserved materials
Application to clinical practice		easy	difficult except for clinical trials
Cost		less expensive	expensive
Course of action		Standardization with more sensitive combination of markers is required to improve the detection limit.	Is application of ASO-RQ-PCR practical? (HTS is ideal.)

Uchiyama T et al. 2020

Kombinace léčiv a MRN – pro a proti

Protocol

- Phase 2 Ven+Ibr; MRD cohort (n=164)
- Pts with confirmed MRD– (in both PB and BM) after 12C Ven+Ibr randomized 1:1 to Pbo or Ibr
- Pts without confirmed MRD– randomized 1:1 to Ibr or Ven+Ibr

Population

- Patients <70 y, previously untreated CLL/SLL
- Median age 58 y; 20% del(17p) or *TP53*^{mut}; 17% del(11q); 19% complex karyotype; 60% *IGHV*^{unmut}

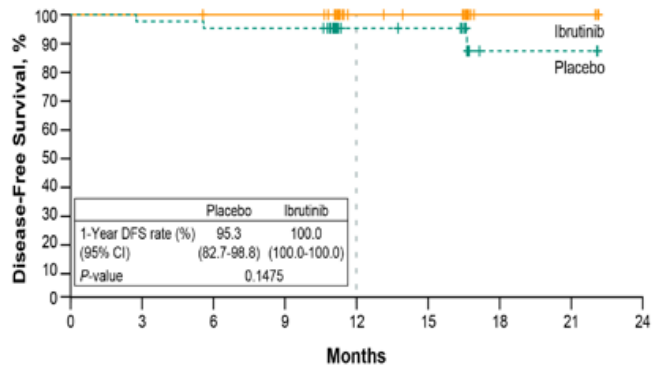
Authors' conclusions

- 1L Ven+Ibr confers high rates of PB and BM MRD– in pts with CLL
- 1-year DFS was similar in pts randomized to Pbo vs Ibr after Ven+Ibr, supporting a FTD that offers treatment-free remissions in pts with CLL/SLL
- Depth of response is reflected in the 30-mo PFS rate of ~95% across all treated pts
- Safety profile for Ibr+Ven was consistent with known AEs for Ibr and Ven, with no new safety signals

PFS Rates by Randomized Treatment Arm

	30-mo PFS % (95% CI)
Pts with confirmed MRD–	
Placebo (n=43)	95.3 (82.7–98.8)
Ibr (n=43)	100.0 (100.0–100.0)
Pts without confirmed MRD–	
Ibr (n=31)	95.2 (70.7–99.3)
Ven+Ibr (n=32)	96.7 (78.6–99.5)

DFS by Randomized Treatment Arm in Confirmed MRD– Group



*The 3 DFS events in placebo arm were disease progression in 2 patients and MRD relapse in 1 patient.

Safety:

- AEs similar across randomized treatment arms
- Across all pts, most common Grade 3/4 AEs (≥5% of pts) were neutropenia (36%), hypertension (10%), thrombocytopenia (5%), and diarrhea (5%)

Wierda et al. ASH 2020

Kombinace léčiv a MRN – pro a proti

Acalabrutinib + venetoklax + obinutuzumab

Protocol (NCT03580928)

- Phase 2 IIS; updated efficacy and safety with sequential AVO (19-month follow-up)
- Enrollment now restricted to patients with *TP53*-aberrant TN CLL
- MRD-guided treatment duration
- **Primary endpoint:** Rate of BM MRD– CR at C16D1

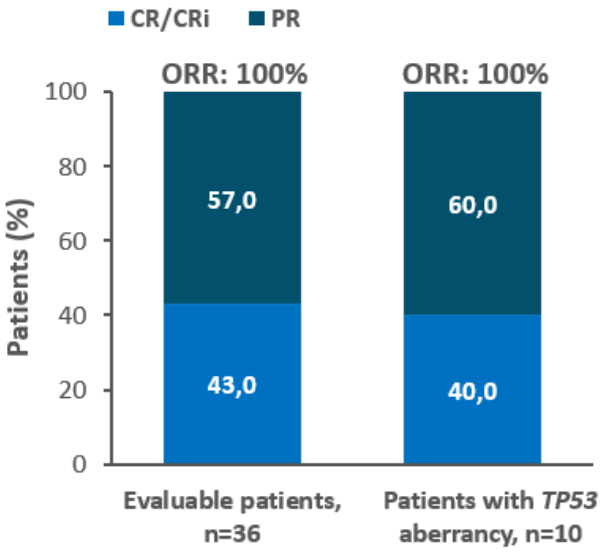
Population

- Median age: 63 years (range, 41–78)
- 39% *TP53* aberrant*; 27% del(11q); 66% *IGHV*^{unmut}; 20% CKT†
- N=44

Authors' conclusions

- AVO is highly active, with 78% achieving BM MRD– CR after 15 months of time-limited therapy in a TN population including ~40% patients with *TP53* aberrancy
- Safety profile of AVO is favorable

Response rate at C16



Primary endpoint: 31% BM MRD– CR at C16

11 patients with BM MRD– CR d/c therapy after 15 cycles per protocol; median time off therapy: 4 months. No patients with PD to date

Efficacy

- PB MRD– and BM MRD– at C16 in ITT: 84% and 78%, respectively; in patients with *TP53* aberrancy: 90% and 70%, respectively
- Response and rates of MRD– did not differ by *IGHV* mutational status

Safety

- Grade ≥3 heme toxicities: neutropenia (34%); thrombocytopenia (23%); anemia (4.5%)
- One case of Grade 3 AF (2%); no major bleeding or febrile neutropenia
- Transient Grade 3 laboratory TLS occurred in 2 patients (4.5%) after starting O (prior to V)

Davids et al. ASH 2020

Budoucnost?

Veneto-STOP studie

Study Overview

Key Eligibility: Patients with CLL/SLL, currently receiving venetoclax as monotherapy or with an anti-CD20 antibody (1L or relapsed), 2x MRD– PB assessments at least 28 days apart

Primary Objective:

- To utilize MRD assessment with a NGS assay (clonoSEQ®) to guide clinical decision making in patients with CLL receiving venetoclax-based regimens

Primary Endpoints:

- Proportion of patients able to remain off venetoclax-based therapy at 12 cycles following treatment discontinuation

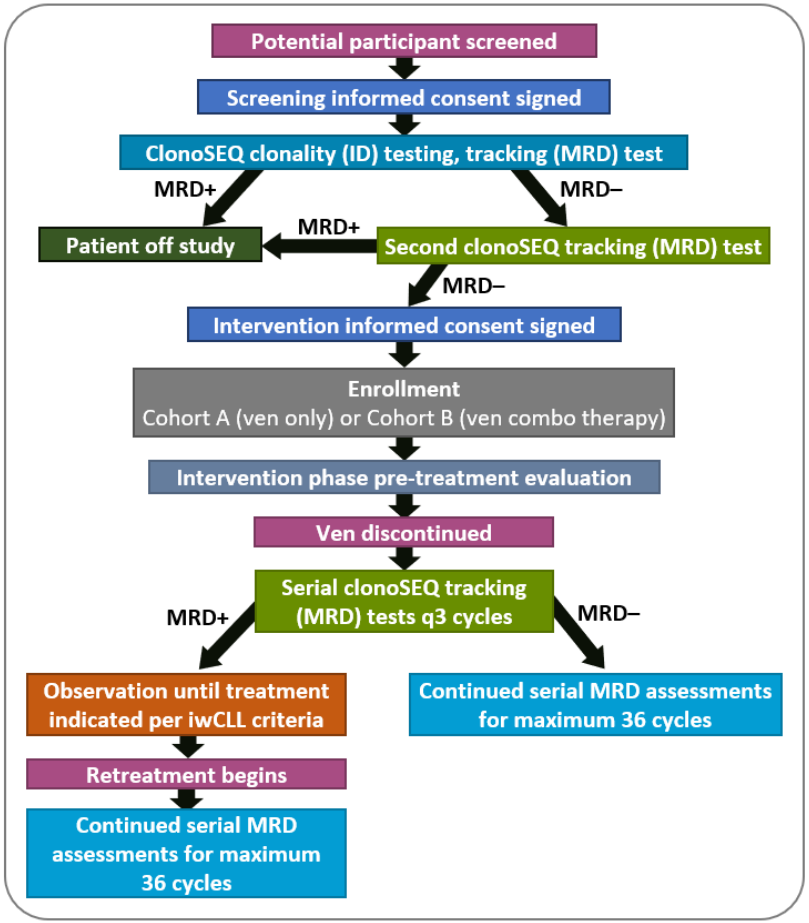
Key Secondary Endpoints:

- Incidence of MRD+ during 36-cycle observation period following venetoclax discontinuation
- Incidence of new therapy initiation during observation period
- PFS and OS from start of treatment-free observation

Should a patient require re-treatment, endpoints include ORR, CR rate, MRD– rate, and AEs for venetoclax-based therapy re-treatment (health-related outcomes including cost and QoL will be assessed)

- * 1 cycle = 28 days.

Study schema: Multicenter Phase 2 Trial



- The ClonoSEQ® ID test will be performed, followed by the ClonoSEQ® MRD assay to evaluate MRD in the PB at two time points (≥28 days apart)
- Patients who have received ≥6 months ven and achieve uMRD (defined as $<10^{-5}$) will enter a period of treatment-free observation
- Monitoring with serial MRD assessments on PB will occur every 3 cycles* for 36 cycles
- Patients will undergo retreatment upon PD requiring therapy (per iwCLL criteria)
- Assessments for retreated patients will continue for 12 cycles or to the end of 36 cycles from the time of treatment free observation (whichever occurs first)

Summary:

- Study will enrol 80 patients
- This trial will explore whether the duration of venetoclax therapy should be individualized, based on the depth of response achieved, and not used on a fixed duration schedule

- Ujjani CS, *et al.* ASH 2019; Abstract 1758.

Ujjani et al. ASH 2020